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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VAKILI, ZOHREH	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,150	MUNN ET AL.	
	Examiner	Art Unit	
	Zohreh Vakili	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,17-27,42 and 43* is/are pending in the application.

4a) Of the above claim(s) *1,4,5,27 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-10,17-26 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :9/20/2004, 12/6/2004, 5/24/2005, 11/10/2005, 12/19/2006, 03/20/2007, 05/03/2007.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IX (claim 42) in the reply filed on 12/19/2006 is acknowledged. The traversal is on the ground(s) that claims 2, 3, 6-10, and 17-26 are also drawn to methods of treating cancer comprising administering an inhibitor of indoleamine-2,3-dioxygenase and at least one additional chemotherapeutic agent and therefore belong in Group IX. This is argument is persuasive and claims 2, 3, 6-10, and 17-26 are rejoined and will be examined with the elected group.

Applicants further request the rejoinder of Groups I, II, IX and X. Applicants argue that the burden to search and examine a method of augmenting tumor rejection with the elected method of treating cancer is not unduly burdensome. This argument is not persuasive. The restriction of claims 1, 4, 5, 27, and 43 is maintained for the reasons of record. Firstly, claims drawn to "augmenting the rejection of tumor cells" and "stimulating an immune response" are distinct from methods of treating cancer. The methods of treating cancer as instantly claimed require administration to a subject and require that the subject have cancer. However, claims drawn to methods of augmenting tumor rejection or method of stimulating an immune response are not limited to malignant tumors. As such, the search required for these methods is broader than that required for cancer.

Group IX (claim 42) is rejoined with claims 2, 3, 6-10, and 17-26. Non-cancelled claims rejoined with Group IX will be examined to the extent that they are drawn to methods of treating cancer.

The restriction of Groups I, II, IX, and X is still deemed proper and is made **FINAL**. Claims 1, 4, 5, 27, and 43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/19/2006.

Status of the Claims

Claims 1-10, 17-27, 42-43 are currently pending and are the subject of this Office Action. Claims 1, 4-5, 27, 43 are withdrawn from further consideration. Claims 2, 3, 6-10, 17-26, and 42 are presently under examination. This is the first Office Action on the merits of the claims.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 9/20/2004, 12/6/2004, 5/24/2005, 11/10/2005, 12/19/2006, 03/20/2007, and 05/03/2007.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The residence of Andrew Mellor has been crossed out and changed to a different address but this alteration is neither initialed nor dated.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 6-10, 17-26, and 42 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn to methods of treating cancer comprising administration of "an inhibitor of indoleamine-2,3-dioxygenase" (IDO). The specification discloses four examples of inhibitors of indoleamine-2,3-dioxygenase (*e.g.*, page 15, lines 1-8), which include 1-methyl-tryptophan (1MT), beta-(3-benzofuranyl)-alanine, beta-[3-benzo(b)thienyl]-alanine and 6-nitro-tryptophan. The specification also discloses that the inhibitor may be the D or L isomer of an inhibitor of indoleamine-2,3-dioxygenase

(*id.*). The specification does not disclose any other inhibitors of indoleamine-2,3-dioxygenase as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a recitation of "inhibitor of indoleamine-2,3-dioxygenase". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to the DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *Lilly*. The court stated that, "[A] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " *Lilly* at 1567, 43 USPQ2d at 1405. The court also stated that:

> "[A] generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA' without more, is not an adequate written description of the genus because it does not

> distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." *Id.* at 1568, 43 USPQ2d at 1406.

The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.*

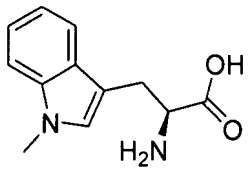
The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying

characteristics, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis added, bracketed material in original).

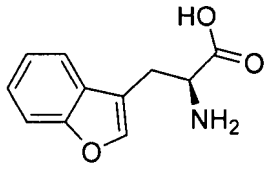
While the inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here (which are drawn to inhibitors only defined by their activity). The instant specification may provide an adequate written description of inhibitors of indoleamine-2,3-dioxygenase, per *Lilly*, by structurally describing representative inhibitors of indoleamine-2,3-dioxygenase (*e.g.*, specific inhibitors, structures, etc.), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe inhibitors of indoleamine-2,3-dioxygenase useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. The specification discloses four specific inhibitors: 1-methyl-tryptophan (1MT), beta-(3-benzofuranyl)-alanine, beta-[3-benzo(b)thienyl]-alanine and 6-nitro-tryptophan as IDO inhibitors. However, this does not provide a description of the

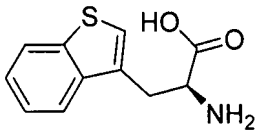
broadly claimed "inhibitor of indoleamine-2,3-dioxygenase" that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features (*e.g.*, what specific structural feature(s) impart IDO inhibitory activity). It is noted that the four inhibitors explicitly disclosed are all derivatives of alanine and tryptophan with distinct, unrelated chemical substituents and modifications (*e.g.*, $-NO_2$, methyl, 3-benzofuranyl, 3-benzo(b)thienyl).



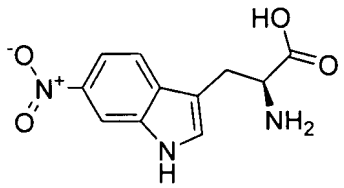
1-methyl-tryptophan



b-(3-benzofuranyl)-alanine



b-[3-benzo(b)thienyl]-alanine



6-nitro-tryptophan

As such, it is not apparent that any particular structural feature imparts the biological activity (inhibition of IDO) of these compounds. In view of the above, the instantly claimed inhibitors of indoleamine-2,3-dioxygenase are clearly not adequately described by a functional characteristic (IDO inhibition) coupled with a structural feature which impart said functional characteristic. Further, the specification also fails to describe inhibitors of indoleamine-2,3-dioxygenase by the test set out in *Lilly* because the specification only describes four specific compounds. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of inhibitors of indoleamine-2,3-dioxygenase that is required to practice the claimed invention.

Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn to "vaccine[s]". The specification discloses examples of vaccines (*e.g.*, page 16, lines 6-9), which include anti-viral vaccines and tumor vaccines. The specification also discloses three examples of anti-viral vaccines (HIV, tuberculosis and malaria vaccines) and four examples of "tumor vaccines" (melanoma, prostate cancer, colorectal cancer and multiple myeloma vaccines). The specification does not disclose any other vaccines as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a recitation of "vaccine" or "tumor vaccine". Accordingly, in the absence of sufficient

recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Applicants are directed to the discussion of *Lilly* and *Enzo*, *supra*.

While the inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here (which are drawn to vaccines and tumor vaccines). The instant specification may provide an adequate written description of "vaccine" or "tumor vaccine" per *Lilly*, by structurally describing representative vaccines (*e.g.*, by name, structure, etc.), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe vaccines useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification generically discloses “anti-viral vaccines” and “tumor vaccines”, this does not provide a description of the broadly claimed genus that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features (*i.e.*, of what are the vaccines composed). Further, the specification also fails to describe vaccines by the test set out in *Lilly* because the specification describes only three generic types of anti-viral vaccines and four generic

types of tumor vaccines (but provides no *specific* vaccines). Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of vaccines or tumor vaccines that is required to practice the claimed invention.

Claims 23-25 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn to "immunogenic peptides" and "genetically modified tumor cells or genetically modified cell lines". The specification discloses examples of immunogenic peptides (*e.g.*, page 16, lines 15-16), which include immunogenic HIV peptides, immunogenic tumor peptides or immunogenic human cytomegalovirus peptides. The specification also discloses one example of a genetically modified tumor cell (GM-CSF; *id.* at lines 17-19). The specification does not disclose any other immunogenic peptides or genetically modified tumor cells as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is a recitation of "immunogenic peptides" and "genetically modified tumor cells". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genera.

Applicants are directed to the discussion of *Lilly* and *Enzo*, *supra*.

While the inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here (which are drawn to peptides and genetically modified tumor cells). The instant specification may provide an adequate written description of "immunogenic peptides" or "genetically modified tumor cells", per *Lilly*, by structurally describing representative peptides or modified tumor cells (*e.g.*, specific peptides, amino acid sequences, cell lines, etc.), or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe immunogenic peptides or genetically modified tumor cells useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification generically discloses immunogenic HIV peptides, immunogenic tumor peptides or immunogenic human

cytomegalovirus peptides as immunogenic peptides, this does not provide a description of the broadly claimed genus that would satisfy the standard set out in *Enzo* because the specification provides no functional characteristics coupled to structural features (*i.e.*, what amino acid sequences, for example, make a peptide immunogenic). Similarly, with respect to the genetically modified tumor cells, there is no description of how these tumor cells are modified or with what they are modified. Further, the specification also fails to describe immunogenic peptides or genetically modified tumor cells by the test set out in *Lilly* because the specification describes only three generic types of immunogenic peptides (but provides no sequences). Similarly, only one genetically modified tumor cell is described (GM-CSF). Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of immunogenic peptides or genetically modified tumor cells that is required to practice the claimed invention. It is noted that a "peptide" is a compound comprising two or more amino acids in which a carboxyl group of one is attached with the amino group of another. Clearly, the structure of a "peptide" that is immunogenic is not adequately described, including the sub-genera specifically recited in the specification.

Claims 2-10, 17-26, and 42 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating melanoma comprising administering 1-methyl-tryptophan and cyclophosphamide, does not reasonably provide enablement for the treatment of all cancers by administering any inhibitor of

indoleamine-2,3-dioxygenase combined with any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of cancer and inhibition of tumor growth comprising administering an inhibitor of indoleamine-2,3-dioxygenase in combination with a chemotherapeutic agent. The specification and claims state that such a combination will be synergistic (*i.e.*, the effect of the combination is greater than that of either agent alone). The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

Also with respect to unpredictability of treating cancer with the claimed drug combinations, Examiner refers to Muller *et al.* (Expert Opin. Ther. Targets, 2005, vol. 9, no. 4, pages 831-849). Muller *et al.*, cited for evidentiary purposes, teaches that chemotherapeutic drugs have been used in combination with 1-methyl-tryptophan (1-MT) to treat experimental tumors in the MMTV-Neu model of breast cancer (page 835). While some drugs were "cooperative" with 1-MT, many others were not. For example, cisplatin, cyclophosphamide and doxorubicin (DNA damaging agents) exhibited cooperativity, but the antimetabolites 5-fluorouracil and methotrexate did not. However,

vinblastine (also an antimetabolite) did show cooperativity. Rapamycin also showed no cooperativity whereas a farnesyl transferase inhibitor did. The authors conclude (page 844) that, "it is notable that IDO inhibition cooperated with all of the DNA-damaging agents, but none of the antimetabolic agents tested". Thus, it is clear that not all chemotherapeutic agents will be "cooperative" with inhibition of indoleamine-2,3-dioxygenase in the treatment of cancer.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers. Further, it is not at all predictable that any particular combination of drugs will demonstrate synergism.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of cancer generally with any inhibitor of indoleamine-2,3-dioxygenase in combination with any chemotherapeutic agent. Others, such as claims 8-12 and 13, are narrower, reciting specific inhibitors of indoleamine-2,3-dioxygenase and specific cancers, respectively. All, however, are extremely broad insofar as they disclose the general treatment of cancer and tumors with the same combination of compounds, wherein such combination must be synergistic.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (dosages, timing, administration routes, etc.) necessary to treat all of the various cancers and tumors claimed, particularly in humans. The working examples are limited to one particular inhibitor of indoleamine-2,3-dioxygenase (1-methyl-tryptophan) in combination with one particular chemotherapeutic agent (cyclophosphamide) in the treatment of one particular cancer (melanoma). Thus, the applicant at best has provided specific direction or guidance only for the treatment of melanoma with 1-methyl-tryptophan and cyclophosphamide. No reasonably specific guidance is provided concerning useful therapeutic protocols for any other cancers or tumors with any other combination of indoleamine-2,3-dioxygenase inhibitor and chemotherapeutic agent. This is especially true given the unpredictability in the art, as noted *supra*.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that a combination of an inhibitor of indoleamine-2,3-dioxygenase and a chemotherapeutic agent could be predictably used as a synergistic treatment for all cancers as inferred in the claims and contemplated by the specification.

It is generally not predictable that any particular drug combination will have a synergistic effect. Further, the claimed invention is extremely broad, encompassing any

inhibitor of indoleamine-2,3-dioxygenase in combination with any chemotherapeutic agent. Chemotherapeutic agents have different mechanisms and are generally used to treat different cancers and patient populations. As such, one cannot readily predict which chemotherapeutic agents will be synergistic with an inhibitor of indoleamine-2,3-dioxygenase.

Further, Applicants state that 1-methyl-tryptophan is not an efficient inhibitor of indoleamine-2,3-dioxygenase (page 29, line 22) and a racemic mixture is only partially effective in reversing IDO-mediated inhibition of T cell proliferation (*id.* at lines 23-24). Thus, it appears that stereochemistry may play an important role in a compound's ability to inhibit indoleamine-2,3-dioxygenase and that even inhibitors of indoleamine-2,3-dioxygenase are not always effective in reversing IDO-mediated inhibition of T cell proliferation.

There is limited guidance provided in the specification with respect to what particular indoleamine-2,3-dioxygenase inhibitor/chemotherapeutic combinations would be expected to have a synergistic effect in treating cancer or tumors. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-3, 6-10, 17-26, and 42 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 00/66764 (Published 11/9/2000), hereinafter "WO '764".

The instant claims are drawn to methods of treating cancer administering an inhibitor of indoleamine-2,3-dioxygenase. Dependent claims further limit claims to specific inhibitors (*e.g.* 1-methyl-tryptophan) and specific therapeutic agents (*e.g.* vaccines).

WO '764 teaches methods for increasing T cell proliferation comprising administering a tryptophan-enhancing agent (Abstract). Suitable tryptophan-enhancing agents include inhibitors of indoleamine-2,3-dioxygenase (IDO) (page 1, lines 18-21). Preferred IDO inhibitors include 1-methyl-tryptophan, beta-(3-benzofuranyl)-alanine and beta-[3-benzo(*b*)thienyl]-alanine (page 2, lines 12-15 and page 6, line 30 to page , line 10). The reference thus teaches the IDO inhibitors recited in instant claims 2-3. The reference further teaches methods of treating cancer (page 3, lines 30-33; page 18, lines 4-19 and lines 25-29). The IDO inhibitors can be administered as a component of an immune response modulation composition, *i.e.*, in combination with another therapeutic agent (page 16, lines 22-23). Additional therapeutic agents can include T

cells, antigens (*e.g.*, peptides, proteins), nucleic acids encoding antigens (*id.* at lines 25-27). Cytokines, including GM-CSF are taught to be useful in the immune response modulation compositions (page 17, lines 11-18).

The reference thus teaches the limitations recited in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 10/780,150

Claims 6-10 and 17-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14, 19, 24-31, 33, and 36 of copending Application No. 10/780,797. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass the subject matter claimed in the '797 patent.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner
1614

September 12, 2007

Ardin H. Marschel 9/14/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER